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Inflammation as a mechanism of neuropsychiatric disorders and role of physical activity
Zánět jako mechanismus vzniku neuropsychiatrických onemocnění a role fyzické aktivity

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Prohlášení

Prohlašuji, že jsem závěrečnou práci zpracoval samostatně a že jsem uvedl všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

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Abstract

Psychiatric disorders are becoming an increasing problem and possess a socio-economic burden on societies worldwide. There has been an association between inflammation and psychiatric disorders for some time now, but the causal relationships and mechanisms are not fully understood yet. Better understanding of those mechanisms could help us in dividing patients into different mechanistic subtypes which could react differently to a treatment. That way we could prescribe the most effective treatment depending on the mechanism involved. Inflammation is sensitizing an individual to react in more pro-inflammatory fashion to a stressor leading to chronically inflamed states. This is something that we can observe in an array of mechanisms, which creates many positive inflammatory feedback loops. Those feedback loops are very hard to interrupt, because they reinforce each other, plus the immune system is overreacting to subsequent stressor creating a vicious cycle. This could potentially lead to development of neurodegenerative diseases. As it turns out, physical activity acts on several of those mechanisms involved in inflammatory feedback loops at the same time, making it an ideal prevention/treatment candidate. It plays a huge role in regulation of inflammation in anti-inflammatory manner and might be one of the ways to prevent and treat patients with psychiatric disorders such as major depressive disorder as well as neurodegenerative diseases. This thesis is going to explore relationship between inflammation and mental health. Possible causal relationships between inflammation and psychiatric disorders will be discussed. Mechanisms involved in inflammation regulation, effects of physical activity and inflammation induced pathology observed in psychiatric disorders will be described.

Key words:

Inflammation, psychiatric disorders, neuroinflammation, exercise, chronic inflammation, kynurenine, SIRT1, interleukin 6, brain derived neurotrophic factor

Abstrakt

Psychiatrická onemocnění jsou stále větší problém a způsobují obrovskou socio-ekonomickou zátěž na společnost po celém světě. Asociace mezi psychiatrickými onemocněními a zánětem jsou známy již po nějakou dobu, avšak stále nejsou zcela pochopeny mechanistické a kauzální vztahy. Lepší porozumění těmto mechanismům může vést k rozdělení pacientů do různých skupin podle mechanismů, které by mohly reagovat odlišně na danou léčbu. Na základě tohoto rozdělení bychom mohli stanovit tu nejefektivnější léčbu. Zánětlivost dělá jedince citlivější a díky tomu pak následně reaguje více pro-zánětlivým způsobem na další příchozí stresory, což pak vede ke chronicky zvýšené zánětlivosti. Tohle je něco, co můžeme pozorovat v celém spektru mechanismů, které vytvářejí pozitivní zpětnovazebné smyčky. Tyto smyčky se velice těžko přerušují, protože se navzájem podporují, když k tomu přidáme organismus, který přehnaně reaguje na další stresory, vytváří to začarovaný kruh. Potencionálně to může vést k vývoji neurodegenerativních onemocnění. Jak se ukazuje, fyzická aktivita je v najednou ovlivňuje několik mechanismů zapojených v zánětlivých procesech a zpětnovazebných smyčkách, a to z ní dělá ideálního kandidáta na prevenci a léčbu. Hraje velmi důležitou roli v proti-zánětlivých procesech a mohl by to být jeden ze způsobů, jak léčit pacienty s psychiatrickými onemocněními jako je depresivní porucha, nebo neurodegenerativní onemocněními. Tahle práce se bude zabývat vztahem mezi zánětlivostí a mentálním zdravím. Oddiskutujeme možným kauzální vztah mezi zánětlivostí a psychiatrickými onemocněními. Také se pokusíme objasnit účinky fyzické aktivity na zánětlivost a na zánětlivostí vyvolané patologie, které můžeme pozorovat u psychiatrických onemocnění.

Key words:

Inflammation, psychiatric disorders, neuroinflammation, exercise, chronic inflammation, kynurenine, SIRT1, interleukin 6, brain derived neurotrophic factor

Contents

1 Table of abbreviations

CRH - activating corticotropin-releasing hormone
AD - Alzheimer's disease
Aß - amyloid beta
BDNF - Brain derived neurotrophic factor
CNS - central nervous system
CSF - cerebral spinal fluid
CRP - C-reactive protein
DAMP - damage-associated molecular patterns
FNDC5 - fibronectin type III domain-containing protein 5
GC - glucocorticoids
HPA - hypothalamic-pituitary-adrenal
IR- immune reaction
IDO - indoleamine 2,3-dioxygenase
IFN- γ - interferon gamma
IFN- β - interferon β
IFN-α - interferon-α
IL-10 - interleukin 10
Il-1β - interleukin 1β
IL-6 - interleukin 6
KAT - kynurenine aminotranferase
KP - kynurenine pathway
KYNA - kynurenic acid
LPS - lipopolysaccharide
MDD - major depressive disorder
miRNA - microRNA
NMDA - N-methyl-D-aspartate
Nrf2 - nuclear factor erythroid 2–related factor 2
NF-κB - nucleat factor κB
PA - physical activity
PRR - pattern recognition receptors
PAMP - pattern-associated molecular patterns
PGC - peroxisome proliferator-activated receptor-gamma coactivator
PTSD - post-traumatic stress disorder
PFC - prefrontal cortex
QUIN - quinolinic acid
ROS - reactive oxygen species
RSD - repeated social defeat
SSRI - selective serotonin reuptake inhibitors
SIRT1 - silencing information regulator
STAMP-2 - six-transmembrane protein of prostate 2
SNS - sympathetic nervous system
TrkB - tropomyosin-related kinase B
TNFα - tumor necrosis factor α
VEGF - vascular endothelial growth factor

2 Introduction

Depression and anxiety disorders are globally estimated that as much as 8% of the population and 16% of Americans are affected at least once during their lifetime. It is also one of the leading causes of disability worldwide (James *et al.*, 2018). These disorders may be perceived as a less of a problem for the individual and society than many other medical conditions, but quality of life of these individuals is often lower than of those with other medical conditions (Bonicatto *et al.*, 2001). This possesses a huge socioeconomic burden on societies worldwide (Sartorius, 2001; Greenberg *et al.*, 2015). Current most frequent treatment of psychiatric disorders is pharmacological. Although this treatment is having some success, it often has side effects and in many cases is not much more successful than placebo (Cipriani *et al.*, 2016, 2018). The response rate is around 50% and remission rate around 30% to the treatment (Trivedi *et al.*, 2006). There is an increasing evidence of inadequate activation of immune system in psychiatric disorders which might be one of the underlying mechanisms. Inflammation has been suggested to play a role in these disorders. There are already known associations between inflammatory markers and psychiatric disorders (Dowlati et al., 2010; Khandaker et al., 2015;Grzybkowska, Anczykowska, Pyczek, & Żychowska, 2018), but causal links are yet to be fully understood and established. This thesis is going to focus on exploration and elucidation of some of the potential causal relationships.

2.1 Inflammation

Inflammation is something we would not be able to live without. It plays a major role in our immune system, repair tissue damage as well as protect us from pathogens. As with anything, too much of one thing is a bad thing and inflammation is not an exception. If the inflammatory stimulus is resolved, homeostasis and normal function prevail, though when it is not the chronic inflammatory state occurs, it is detrimental to our health as we can see in many auto-immune diseases where that happens. Literature is pointing towards inflammation as being part of the root cause of many diseases including mood and psychiatric disorders. The challenge here is to establish what causes what and how that might potentially help us in treating those disorders. Physical activity (PA) plays a huge role in regulating many different aspects of our physiology including endocrine system and immune function. As it turns out PA might be a potential prevention tactic and part of a treatment of psychiatric and neurodegenerative diseases with minimal side effects, or even positive ones. Apart from that, exercise promotes vascular health, neuroprotection, neuroplasticity and improve cognitive function, which is especially important in aging population and people with

neurodegenerative diseases (Ahlskog *et al.*, 2011). We are going to explore specific mechanisms that might be involved in affecting mood and psychiatric disorders.

3 Inflammatory response to a stressor

Although this is extensively covered in literature, we are going to mention some of the mechanisms involved as they will help us further in the thesis. Inflammation is activated by physiological, environmental or psychological stressors. Environmental and physiological stressors activates pattern recognition receptors (PRR) mainly through pattern-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP) (Janeway, 1989), this then leads to a cascade of reactions triggering immune reaction (IR) (Akira *et al.*, 2006). IR could be also triggered by psychological and psychosocial stress, mainly through activation of sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis (Akira *et al.*, 2006). This stress can in fact activate sterile innate immune reaction which includes DAMPs (Fleshner, 2013*b*), the sterile activation in particular can lead to an inflammatory disease if unresolved. Present in the brain as neuroinflammation it is also involved in Alzheimer's disease (AD) and other neurodegenerative diseases, mainly through inflammasome which can be activated by sterile stimulation of PRRs and then plays a role in production of amyloid beta (Aß), hallmark of AD and further inflammatory processes (Sheedy *et al.*, 2013; Heneka *et al.*, 2015).

4 Evidence of increased inflammation in psychiatric disorders

There is ever increasing evidence of individuals affected by psychiatric disorders having increased inflammatory markers such us interleukin 6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor α (TNFα), while also decreased anti-inflammatory interleukin 10 (IL-10) (Chang et al., 2017; Kahl et al., 2005; Rothermundt et al., 2001;Howren, Lamkin, & Suls, 2009;Cepeda, Stang, & Makadia, 2016; Wium-Andersen, Ørsted, Nielsen, & Nordestgaard, 2013). Although meta-analysis of cytokines in depressed and non-depressed people has shown that only 2 of those cytokines differ significantly between people with depression and without it, those were IL-6 and TNFα (Dowlati *et al.*, 2010). It has been shown that increased levels of inflammatory marker IL-6 has been associated with depression and psychosis, which affects those individuals for a lifetime (Khandaker *et al.*, 2015). Young people could be affected more, because of their development. Increased inflammation could cause metabolic

stress on the brain and other organs, hindering its development (Pruimboom *et al.*, 2015). This is evidence that there is in fact immune dysregulation and activation of the inflammatory response system. Furthermore, as much as 39% patients undergoing treatment of hepatitis C by interferon-α (IFN-α), which is potent pro-inflammatory cytokine, experience moderate to severe depressive symptoms at least once during the treatment (Raison *et al.*, 2005; McNutt *et al.*, 2012). There is also increased incidence of psychiatric comorbidity in immune-mediated inflammatory diseases such as inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis (Marrie *et al.*, 2017), although we have to take in an account psychosocial factors participating to the overall state of the individual, it is certainly interesting data in the light of other evidence of inflammatory mechanisms underlying psychiatric disorders. For example recently, one interesting study showed increased depressive and anxiety symptoms after exposure to endotoxin vs. placebo controlled group (Irwin *et al.*, 2019).

4.1 Inflammation does not equal disorder

It is very important to note that not everyone with higher inflammatory markers has psychiatric problems and not everyone with psychiatric problems has higher levels of inflammatory markers (Dowlati *et al.*, 2010). Although as we have discussed, we can see from the literature that if we compare those with psychiatric disorders to healthy individuals, they do in fact have higher levels of pro-inflammatory markers overall. One suggestion is that depression is not "one size fits all", but rather there are subtypes of depression with different mechanisms involved (Euteneuer *et al.*, 2017). This can also help us identifying patients who might be more responsive to a specific treatment tactic. Patients with psychiatric disorders without elevated inflammatory markers could be potentially more responsive to interventions. The question is: Are those patients more responsive to pharmacological intervention (and which one), because there are perhaps mechanisms which pharmacological treatment could still help them? Are they prone to be more responsive to psychological intervention and placebo? On the other hand, patients with increased inflammatory response could see larger benefit from intervention such as exercise and/or anti-inflammatory treatment as we are going to explore further in this thesis. There are some studies elucidating some of these questions, but more studies are needed to confirm and answer them.

4.2 Trends in literature

We have seen some trends in emerging literature on this topic. Mainly pre-treatment levels of CRP predict response to a treatment. Specifically, we have seen non-response to a treatment by selective serotonin reuptake inhibitors (SSRIs) in patients with depression and

elevated levels of the inflammatory marker CRP, while showing better response to non-serotonergic anti-depressants, on the other hand showing responsiveness to SSRIs in patients with not elevated levels of CRP (Uher *et al.*, 2014; Jha *et al.*, 2017; Chamberlain *et al.*, 2019). One study also showed higher levels of inflammatory markers, especially IL-6 and TNF α in treatment resistant patients with 3 or more failed antidepressants treatment trials compared to 0 or 1 failed antidepressant treatment trial (Haroon *et al.*, 2018). Another study showed elevated levels of CRP prior to treatment predicted elevated clinical responsiveness to lurasidone in patients with bipolar I depression (Raison *et al.*, 2018). There is also evidence that anti-depressant treatment increased anti-inflammatory cytokines in both responsive and non-responsive patients with major depressive disorder (MDD), although pro-inflammatory cytokines stabilized in responsive patients, they continue to increase in non-responsive patients (Syed *et al.*, 2018). This suggests that CRP divides patients into phenotypes of responsiveness to an antidepressant treatment and potential exploration of anti-inflammatory second line treatment.

4.3 Stress sensitization

There is an evidence of significantly increased responses in levels of nuclear factor κB (NF-κB) and IL-6 due to psychosocial stress in individuals with early life stress and MDD compared to controls, furthermore those responses significantly correlated with Hamilton depression scale scores (Pace *et al.*, 2006). Taken together, this provides us with evidence of major dysregulation of IR after repeated stress suggesting a downward spiral towards more inflammatory states as the inflammation increases. This might be one of the reasons why it is so difficult to treat psychiatric disorders in the first place. Once the inflammation is increased for some reason, there is going to be more intense inflammatory responses to a stressor, this effect has been called the stress-sensitization (McLaughlin, Conron, Koenen, & Gilman, 2010; Post, 1992;Luczynski, Moquin, & Gratton, 2015).

5 Inflammation inducing mechanisms

5.1 HPA and SNS axis

IR is caused by a stressor; this stressor could be viral, bacterial, physical and or psychological, latest one being of ever more increasing concern (Liu *et al.*, 2017). We can also see an increase in expression of pro-inflammatory genes (Cole *et al.*, 2007; Grzybkowska *et al.*, 2018). There is evidence for both pro- and anti-inflammatory responses to a stressor through SNS and HPA axis activating corticotropin-releasing hormone (CRH), which then

activates glucocorticoids (GC) that have ability to induce anti-inflammatory responses (Sorrells *et al.*, 2009). Activated GC receptor may have ability to directly bind to pro-inflammatory NF-κB, thus preventing its migration to nuclei and starting a cytokine transcription, but GCs also mediate increases in lipopolysaccharide-induced NF-κB in the prefrontal cortex and hippocampus after exposure to chronic unpredictable stress (Grippo and Scotti, 2013). GCs are causing anti-inflammatory systemic response plus tissue site specific pro-inflammatory one. They act beneficially in keeping homeostasis in a short term, that is also why we see short negative feedback loop with cortisol, but long exposure to GCs is detrimental to homeostasis and can lead to chronic inflammation, cortisol resistance, its circadian release abnormalities and disruption of HPA axis. [From review reference: (Guilliams and Edwards, n.d.)] Repeated stress is going to lead towards dysregulation, disbalance and inability to react appropriately, largely due to changes in GC/catecholamine sensitivity and gene expression (Strahler *et al.*, 2015), which promotes inflammatory response over the anti-inflammatory one. Disrupted HPA axis is negatively going to affect sleep, which proper function is necessary for optimal health and its disruption is another driver of inflammation and neuroinflammation (Xie *et al.*, 2013; Hirotsu *et al.*, 2015). Franco et al., 2016 showed that chronic stress induces HPA axis sensitization in mice. HPA axis sensitization is also hypothesized to play a role in post-traumatic stress disorder (PTSD) and its disruption in psychiatric disorders (Yehuda, 1997; Watson *et al.*, 2004; Vreeburg *et al.*, 2009; Morris *et al.*, 2012). It was also able to predict responsiveness to anti-depressants in some studies (Fischer *et al.*, 2017).

5.2 Downstream signalling pathways

Downstream effect of stimulating inflammatory pathways by PRRs leads to recruitment of neutrophils, macrophages, induction of T-cell adaptive immune response. Most important mediators in those processes are type I interferons as well as NFκB, which then activate expression of pro-inflammatory genes by several different pathways during the PRR stimulation. Stimulation of PRRs also activates mitogen-activated protein kinase cascade, responsible for induction of NFκB pathway. In dendritic cells, stimulation leads to activation of interferon β (IFN- β) gene expression. It also leads to production of reactive oxygen species (ROS) (Takeuchi and Akira, 2010). Activation of capsase-1 leads to activation of inflammasome, which then triggers production and release of interleukin 1β (Il-1β) mainly in macrophages. IL-1β is key mediator of sterile inflammation which is indicated to play a role in many non-microbial inflammatory diseases (Chen and Nuñez, 2010). There is a complex

pro-inflammatory response and this thesis is going to explore some of these mechanisms further.

5.3 Glial Cells

Glial cells, consisting of microglia, astrocytes and oligodendrocytes, are providing a complex function in the central nervous system (CNS) including both pro- and anti-inflammatory processes. What do they do in an inflamed CNS and what are potential mechanisms of inducing psychiatric disorders? Let's say we have already elevated neuroinflammation, microglia are going to be the first to respond by moving towards the trigger of inflammatory response (e.g. breaching of BBB) and release cytokines such as IL-1β, TNF-α, and IL-6 (Jha *et al.*, 2012). Those get recognized by astrocytes, which then release both pro- and anti-inflammatory response, therefore astrocytes are balancing on inflammatory spectrum and there are many mechanisms involved in tilting this spectrum, those mechanisms are not fully understood yet (Zamanian *et al.*, 2012; Pekny *et al.*, 2014; Liddelow *et al.*, 2017) Although it is clear that if the inflamed state persists and turns into chronic inflammation, many damaging processes happen to the CNS such us neuronal damage, degeneration and impaired neuroplasticity, which contribute to psychiatric and mood disorders and loss of function (Kempuraj et al., 2018, 2017; Liddelow et al., 2017; Pekny et al., 2014;Luczynski et al., 2015). Microglia are also susceptible to priming by a stressor, which means their reaction to it is not as intense as to subsequent stressors (Maslanik *et al.*, 2013; Fleshner *et al.*, 2017; Jeon *et al.*, 2017).

5.4 Kynurenine Pathway

One of the processes that neuroinflammation triggers is disruption of L-tryptophan – kynurenine pathway (KP). KP competes with the serotonin one, therefore it is hypothesized that if the KP gets more active, it decreases pool of tryptophan for other monoamines to produce. Although monoamine hypothesis has largely been disputed for the most part and there is lack of evidence to support that it would be the main contributor to psychiatric diseases, it much rather looks like combination of many different mechanisms, also there has not been the evidence that activity of KP would decrease serotonin levels in the brain [for reviews reference: (Boku *et al.*, 2018; Jesulola *et al.*, 2018)].

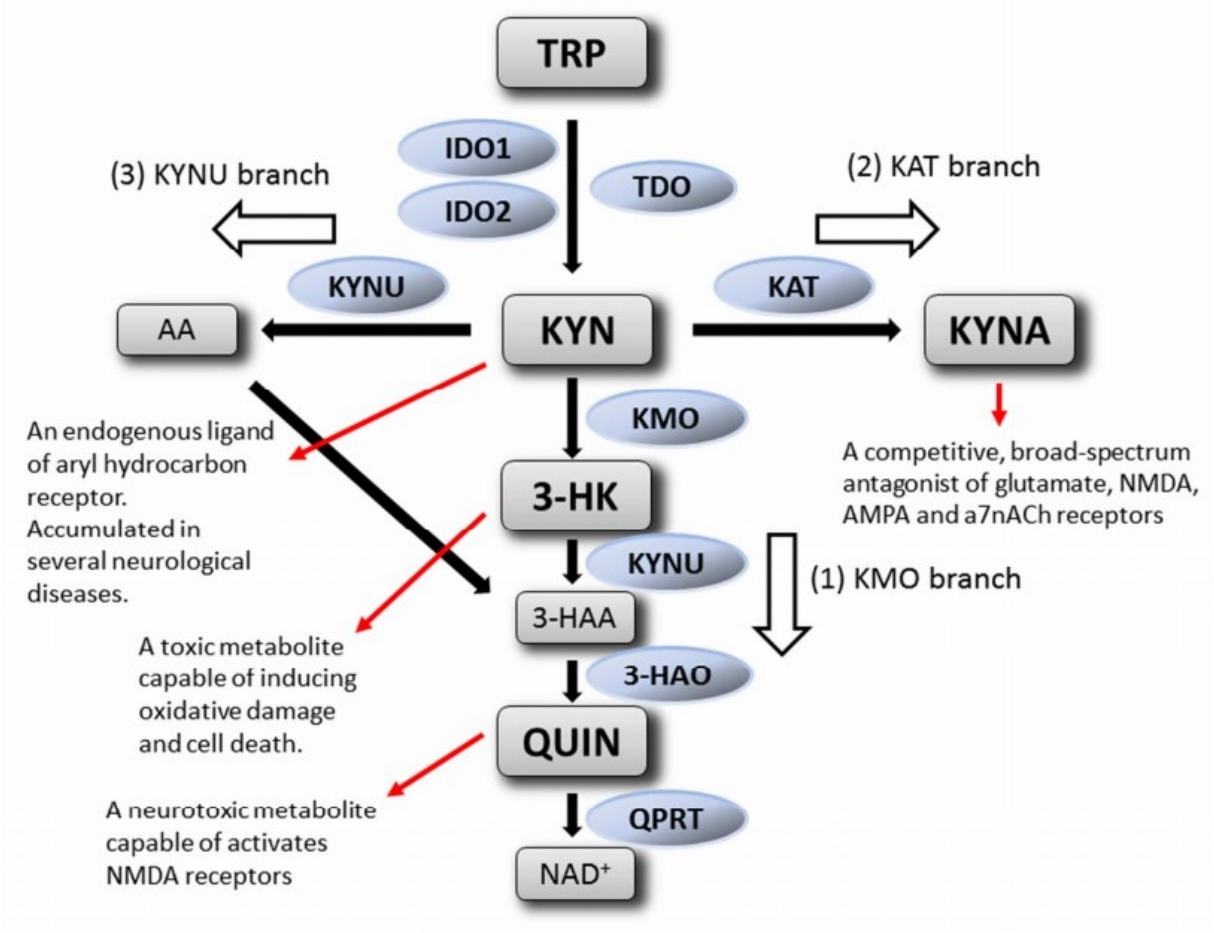

Figure 1: Simplified diagram of the major components of the KP. TRP, tryptophan; KYN, kynurenine; KYNA, kynurenic acid; AA, anthranilic acid; 3-HK, 3-hydroxykynurenine; 3-HAA, 3-hydroxyanthranilic acid; QUIN, quinolinic acid; NAD+, nicotinamide adenine dinucleotide; IDO1, indoleamine 2,3-dioxygenase 1; IDO2, indoleamine 2,3-dioxygenase 2; TDO, tryptophan 2,3-dioxygenase; KAT, kynurenine aminotransferase; KYNU, kynureninase; KMO, kynurenine 3-monooxygenase; 3-HAO, 3-hydroxyanthranilate 3,4-dioxygenase; QPRT, quinolinic acid phosphoribosyl transferase. [Note: full figure reference in "references", reprinted from (Fujigaki *et al.*, 2017)]

5.4.1 Inflammation induced activation

KP gets more active in inflammatory diseases and also psychiatric disorders (Crowley *et al.*, 1992; Guillemin, 2012; Kegel *et al.*, 2014; Kindler *et al.*, 2019). Along the same note, depressive and anxiety like behaviour were also seen in mice, treated with poly I:C which induced inflammatory response characterized by elevated cytokines IL-1β, TNF-α and IL-6, alongside with increased activity of KP in prefrontal cortex (PFC) (Gibney *et al.*, 2013). Activation of KPs is induced by activation of indoleamine 2,3-dioxygenase (IDO). Expression of IDO is induced mainly by interferon gamma (IFN- γ) and STAT1 which activates IDOs

promoter, furthermore TNF-α activation stimulates NFκB pathway, enhancing IFN- γ effect by upregulating IFN- γ receptors suggesting heavily mediated activation by inflammation (Yeung *et al.*, 2015).

5.4.2 Effects of kynurenine pathway on the brain

Activity of KP is related to dorsolateral PFC volume and attention in schizophrenia patients (Kindler *et al.*, 2019). Although this isn´t confirming that kynurenine metabolites are in fact responsible for this effect, because increased in activity of kynurenine has been linked only to a subgroup of patients (40%) which also had elevated cytokine levels, therefore we do not know if the effect is of cytokines or kynurenine (Kindler *et al.*, 2019). Although activity of KP has diverse effects, kynurenic acid (KYNA) metabolite is considered more neuroprotective, but also N-methyl-D-aspartate (NMDA)-receptor antagonist, and counter to quinolinic acid (QUIN), another metabolite which acts as a pro-inflammatory mediator, neurotoxin and also NMDA-receptor agonist(Crowley *et al.*, 1992; Guillemin, 2012). In fact levels of QUIN in cerebral spinal fluid (CSF) has been associated with depressive behaviour and suicidal attempts, on the other hand CSF KYNA was associated with Montgomery Asberg Depression Rating Scale, Suicide Assessment Scale, relapsing-onset of multiple sclerosis and bipolar disorder, therefore the lower KYNA the worse depressive and suicidal symptoms (Rejdak *et al.*, 2002; Bay-Richter *et al.*, 2015; Savitz *et al.*, 2015; Birner *et al.*, 2017). On the other hand, elevated KYNA is associated with schizophrenia (Linderholm *et al.*, 2012; Chiappelli *et al.*, 2014, 2018; Plitman *et al.*, 2017), therefore we are seeing some type of U shape relationship between KYNA and pathology. What seems important is not KYNA or QUIN levels themselves, but rather ratio between them as QUIN does damage the brain and also impairs memory, KYNA on the other hand has the ability to mitigate those effects of QUIN (Beninger *et al.*, 1986; Miranda *et al.*, 1997; Pierozan *et al.*, 2018). QUIN also alters activity in nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, 512 genes which are important in dealing with reactive oxygen species (ROS) and affects inflammation, KYNA has been shown to elevate Nrf2 (Ferreira *et al.*, 2018). Taken together, it seems that specific balance between QUIN/KYNA is important for proper functioning, not only we can see disruption and disbalance of metabolites associated with pathological conditions and diseases, but also cause and effect of those metabolites which elucidate some of the mechanisms on which they act upon and cause these conditions.

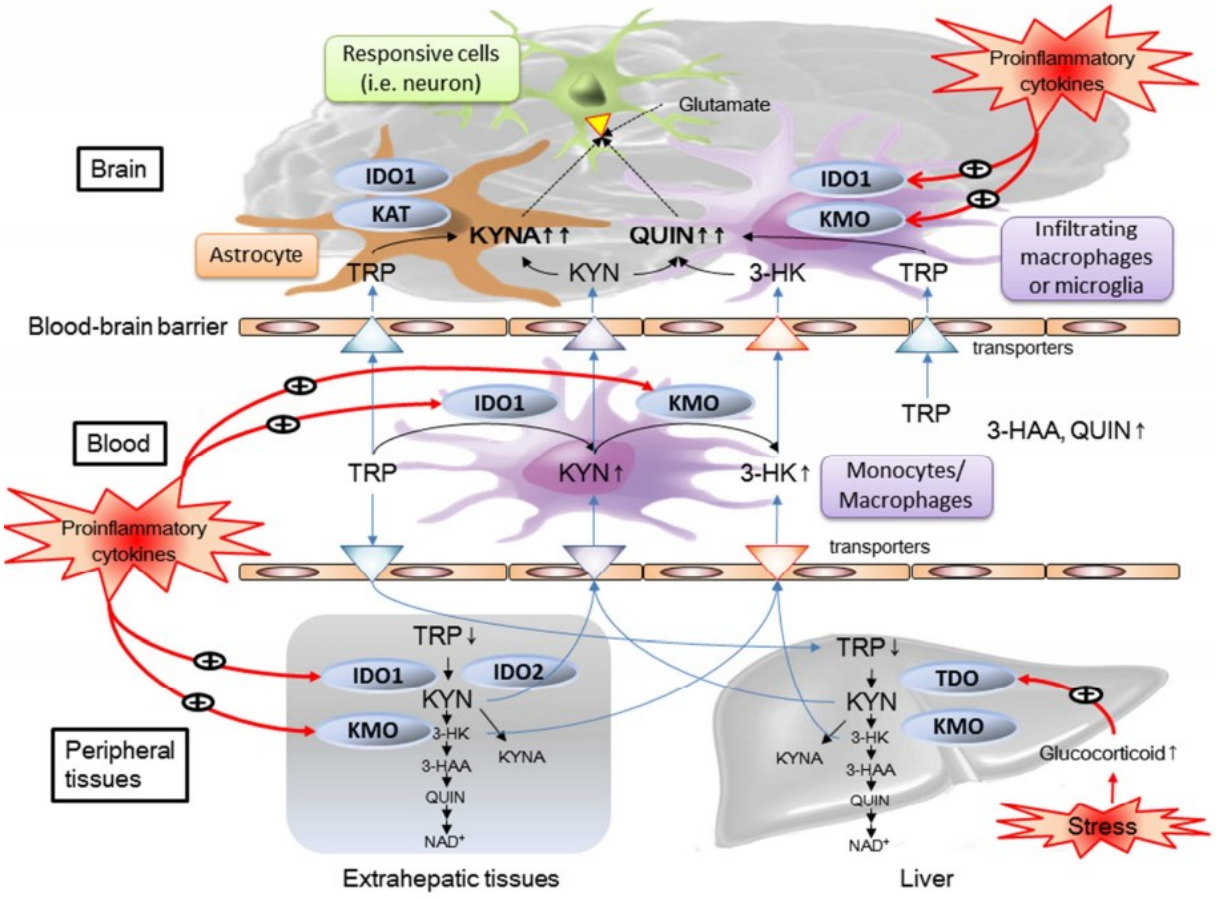

Figure 2: Cell type differences in KP enzyme expression and interactions between peripheral and central kynurenines under inflammatory conditions. Because an excess of peripheral KYN and 3-HK can be transported across the BBB, they can be metabolized by infiltrating macrophages or activated microglia within the CNS. Macrophages and microglia express KMO; therefore, they are responsible for QUIN production in the CNS, which does not easily cross the BBB. In contrast, astrocytes are responsible for the production of KYNA because they predominantly express KAT and are unable to produce QUIN in the CNS because of the lack of or limited amounts of KMO. [Note: full figure reference in "references", reprinted from (Fujigaki *et al.*, 2017)]

5.5 Inflammasomes role in inflammation

NLP3 inflammasome is a multi-protein complex which is part of inflammatory cascade in reaction to both sterile and non-sterile IR (Fleshner, Frank, & Maier, 2017). NLP3 inflammasome is stimulated by NFκB pathway, which plays a role in mediating several inflammatory processes. NLP3 Inflammasome has ability to react to a broad range of stimuli including ATP, K+effux, B-amyloid, silica, uric acid crystals, ROS and potentially PAMPs and DAMPs and plays a role in inducing sterile neuroinflammation (Fleshner *et al.*, 2017).

Inflammasome is activated by repeated stimuli, first stressor primes the inflammasome (Activation of caspase-1, which then cleaves pro-IL-1B and pro-IL-18 into their active form) and subsequent ones activate it (actual release of active IL-1B and IL-18) (Fleshner, 2013*a*; Maslanik *et al.*, 2013; Jeon *et al.*, 2017). IL-1B and IL-18 mediates activity of IDO, therefore activating KP discussed earlier (O'Connor *et al.*, 2009; Maslanik *et al.*, 2013; Yeung *et al.*, 2015; Jeon *et al.*, 2017). IL-1B and IL-18 are also associated with psychiatric disorders (Jeon *et al.*, 2017; Kaufmann *et al.*, 2017) and IL-18 affects activity of HPA axis (Boelen *et al.*, 2004; Sugama and Conti, 2008). Creating yet another pro-inflammatory feedback loop. NLP3 is one of major components in AD as it contributes of build-up of Aß, which then further drives this build up, increasing neuroinflammation (Heneka *et al.*, 2015). Neuroinflammation is underlying most of neurodegenerative and psychiatric diseases and tinkering with some of the inflammatory mechanisms involved could help us with slowing progression of these diseases which possess ever more increasing risk for aging population. It´s been shown that mice without or blocked NLP3 had inability to develop Alzheimer´s disease, were protected against Aß-induced suppression of synaptic plasticity as well as attenuate LPS-induced depressive like behaviors compared to controls (Heneka *et al.*, 2015; Fleshner *et al.*, 2017; Jeon *et al.*, 2017).

5.6 Metabolic Stress induced by inflammation

Chronically increased inflammation is putting metabolic stress on the organism, as immunity is one of the most important systems in human organism; therefore, it has high metabolic priority and cost. That way, it could reallocate some of the energy from organs including brain. That would be another mechanism of action of inflammation causing psychiatric disorders as that is an additional stressor. Pruimboom et al., 2015 present interesting hypothesis; main thought is that in past 30 000 years our brain shrank, and it is hypothesized that partly because we have come to an abundance of food never seen before in human evolution. Part it with the hyperpalatable processed foods in past few decades, therefore we tend to overconsume and eat more frequently, initiating postprandial inflammatory processes (from hypothesis by Pruimboom et al., 2015).

6 Inflammation and Neuroinflammation

How does systemic inflammation, translate onto neuroinflammation? [For a great review reference: (Kempuraj *et al.*, 2017)] Mast cells are immune cells that regulate inflammation

and upon activation release many pro-inflammatory mediators. Systemic-derived pro-inflammatory cytokines/chemokines and other factors can cause breaching of the blood brain barrier (BBB). This allows entrance of those inflammatory mediators including mast cells themselves through the BBB. This creates a stress on CNS, also these peripheral-derived factors and intrinsically generated cytokines/chemokines, α-synuclein, CRH, substance P, Aβ peptide and amyloid precursor proteins can activate glial cells, T-cells and mast cells which in turn induce additional release of the inflammatory and neurotoxic compounds contributing to chronic neuroinflammation and neuronal death. As in the systemic inflammation, there is also a positive feedback loop, where mast cells, glial cells and T cells can reactivate each other to elevate neuroinflammatory condition. Activated glial cells can also recruit monocytes from peripheral blood to increase their number and effect, this so called monocyte trafficking can be turned on by stress and induce anxiety-like behaviour (Wohleb *et al.*, 2015). Chronically inflamed brain can also lead to neurodegeneration and development of neurodegenerative diseases (Heneka et al., 2015; Kempuraj et al., 2019). This is also one of the possible contributions for developing mood and depressive disorders, when the brain is not well, it is very likely that it would contribute to the whole organism of not being well either. It can lead to lowering of brain functions which can be by itself an additional stressor to the individual, because the individual would not be able to deal with difficult situations and process as much information as they normally would. As we have discussed before, when inflammation is increased, individual tend to have stronger pro-inflammatory reaction to a stressor creating an inflammatory positive feedback loop. Weber et al., 2018 showed that sensitizing mice by a stressor, specifically repeated social defeat (RSD) caused accumulation of monocytes and lead to anxiety behaviour recurrence after acute stress up to 24 days after sensitizing, moreover, when RSD-sensitized microglia were removed, it prevented monocyte accumulation and blocked anxiety behaviour, on the other hand removing microglia before RSD-sensitizing did not cause this effect, RSD-sensitized were also more reactive to lipopolysaccharide (LPS) stimulation ex vivo. On a similar note, chronic stress leads to morphological changes specifically decreased dendritic density and retraction of dendritic spines in PFC (Luczynski *et al.*, 2015).

7 Chronic Inflammation

A lot of the evidence from literature so far has been pointing towards a problem with chronic inflammation rather than acute one. As we have discussed, the acute insult if not

resolved would lead to dysregulation and inability to maintain homeostasis, which eventually leads to chronically elevated levels of inflammation and pathology induction. This is something observed on many levels of analysis. HPA and SNS axis, glial cells, KP, inflammasome, sensitization of IR and monocyte trafficking. Apart from these relatively short-term processes, we also see evidence of elevated levels on inflammatory markers or childhood trauma as a predictor of development psychiatric disorder later in life, suggesting that some of these mechanisms persevere over long periods of time, potentially a life time. On a similar note, those with elevated inflammation are sensitized to subsequent stressors, which affect them more, then the first one would, adding up to the inflammation. There are certainly protective mechanisms against those positive feedback loops, but it seems from the literature that they fail to work effectively in today day and age, where there is abundance of stressors all around us (We can count abundance of food into it as well, psychosocial stressors and lack of PA.). Chronic inflammation leads to neurodegeneration, decreased neuroplasticity, lower cognitive function, changes in morphology, changes in volume of brain areas and disrupted brain connectivity (Streit, W. J., Mrak, R. E., & Griffin, 2004; Brunoni *et al.*, 2008; Kapczinski *et al.*, 2008; Monteleone *et al.*, 2008; Wainwright and Galea, 2013; Felger and Treadway, 2017; Ibrahim *et al.*, 2019). Many of those conditions are also seen in patients with psychiatric disorders. Now we are going to focus on what could potentially be caused by the damage done by inflammation and its relation to psychiatric disorders in hypotheses we have not discussed yet.

8 Inflammation induced pathology

8.1 Neuroplasticity

Neuroplasticity is ability of a brain to change and adapt; it is crucial in learning, proper brain circuitry, cell survival, death and morphology. Impairment of neuroplasticity is also one of the candidates thought of as a contributor to psychiatric disorders (Brunoni *et al.*, 2008; Kapczinski *et al.*, 2008; Monteleone *et al.*, 2008). Brain derived neurotrophic factor (BDNF) is considered one of the mediators of neuroplasticity and provides neurogenesis, synaptic transmission, synaptic plasticity, long-term potentiation, cell survival and growth (Yu and Chen, 2011). The ability to adapt, learn and process information is crucial to humans and plays role as one of the coping mechanisms to a stressful event (Brunoni *et al.*, 2008). It has been shown in some studies that pro-inflammatory cytokines affect levels of BDNF negatively (Lapchak *et al.*, 1993; Raetz and Whitfield, 2002; Zhang *et al.*, 2016). Impairment

in neuroplasticity is going to cause additional stress to the individual and inability to cope with the situation properly (Kapczinski *et al.*, 2008). Patients with bipolar disorder have decreased levels of BDNF, which was also associated with their cognitive function (Monteleone *et al.*, 2008). One study suggests changes in neuroplasticity in patients with MDD that depend on brain regions where the tests act upon, moreover it has shown decreased plasticity in hippocampal-neocortical network, on the other hand increased plasticity in amygdala during fear conditioning compared to healthy individuals (Nissen *et al.*, 2010). It goes along with the evidence from literature, that is: cortical and hippocampal decrease in volume and plasticity, while amygdala volume and plasticity increases (Pittenger and Duman, 2008). Apart from that lower levels of BDNF are also associated with neurodegenerative diseases (Connor *et al.*, 1997; Mogi *et al.*, 1999; Michalski and Fahnestock, 2003; Peng *et al.*, 2005; Scalzo *et al.*, 2010; Almeida *et al.*, 2016). Taken together it seems like overall brain plasticity is impaired, but over-stimulation of regions of amygdala due to stress leads to increased amygdala volume and plasticity. As we have discussed earlier, individuals which are sensitized to stress, also show larger impact of future stressors which again all revolve around inflammatory reaction to it. Neuroplasticity piece added to the puzzle suggests not only inflammation increases, but as we can see, subsequent stressors are leading towards over-activation of amygdala, therefore those structures are going to be activated proportionally even more during further stressors compared to other structures e.g. hippocampus and PFC, which in turn decreased in volume and activity.

8.2 Disrupted circuitry

Brain circuitry is another candidate which adds its contribution to the puzzle. We have discussed that amygdala gets bigger and more active compared to other regions in pathology, but what causes that? Disruption in brain circuitry is a clear adept to answer this question. Inflammatory processes discussed so far, play a role in processes of changing brain circuitry. In fact inflammation has been associated with this disruption (Jha *et al.*, 2012; Felger *et al.*, 2016). Similarly, psychiatric disorders were also associated with this disruption (Liao *et al.*, 2012; Tao *et al.*, 2013; Weder *et al.*, 2014; Heshmati and Russo, 2015; Ibrahim *et al.*, 2019). Inflammation induced changes in morphology such as deterioration of dendritic spines, will simply lead to not connected neurons as they are supposed to in a healthy organism. Therefore, neuroinflammation is one of the mechanisms leading towards disruption of these circuits due to the mechanisms described earlier. Proper functioning circuitry is essential for a healthy organism.

9 Introduction – Physical activity

Physical exercise seems to be helping people with psychiatric disorders, but more studies are needed to asses specific mechanisms involved. We now have a robust body of evidence that physical exercise helps in prevention and treatment of people with psychiatric disorders. The challenge here is to identify which of the complex mechanisms are involved in helping those individuals and establish causal mechanisms instead of just relying on associations. This could help us in devising a pharmacological agent or rethinking current state of treatment which could lead towards better efficacy. People are different and react differently to medical and psychological interventions. This is also why we should explore this further, it could help us with identification of those individuals which would benefit the most from pharmacological, psychological, psychiatric or perhaps physical program intervention.

9.1 Importance of PA in youngsters

Not only adults but also adolescent and young adults are affected by depression and is leading cause of disability worldwide(Gore *et al.*, 2011). There is also increasing incidence of both non-suicidal and suicidal self-injury of young adults (Cheung *et al.*, 2013). It has been shown that it might be even more important to prevent psychotic events and mood/anxiety disorders in young adults as those can affect them for a lifetime (McLaughlin *et al.*, 2010; Khandaker *et al.*, 2015). Even more so because of non-responsiveness towards anti-depressant drugs, which have at least questionable efficacy in youngsters, given many times placebo being more effective (Cipriani *et al.*, 2016). Many young people do not recover from a depressive episode even after best evidence based treatment, on the other hand, physical exercise showed prevention and effectiveness in treatment of depression (Pascoe and Parker, 2018). This is also why information and education about these potential risks is more important than ever with children and young adults not being physically active enough to promote health (Riddoch et al., 2004;Kwan, Cairney, Faulkner, & Pullenayegum, 2012).

10 Clinical evidences

PA has been shown to have many benefits for our overall health. Not only does it protect our brain against neurodegenerative diseases and mild cognitive impairment, but it also has potential role in preventing and treating neuropsychiatric and mood disorders (Ahlskog *et al.*, 2011). Individuals who are physically active are rarely affected by mental health disorders. They have relatively high ratio of gene expression of IL-10 to IL-6. This suggests that those individuals are maintaining more of an anti-inflammatory environment than pro-inflammatory

(Grzybkowska *et al.*, 2018). Physical exercise could potentially be used as a treatment of depression or MDD with lower risk of side effects. Patients with MDD have registered robust decrease in depressive symptoms after exercise (Schuch *et al.*, 2016; Morres *et al.*, 2018). Although it is important to note that it was those studies which were using aerobic exercise with moderate to vigorous intensities, with mixed supervised/unsupervised format and supervised by qualified physical exercise professionals were associated with larger antidepressant effect (Schuch *et al.*, 2016).

11 Effect of physical activity on inflammation

PA is a stressor to the body as well, why does it then show decreases in a chronic inflammation? Well, PA is an acute stressor and does cause some of the inflammatory processes to take place. Although those come with adequate threat to the organism, which then the inflammatory processes resolve and deal with the situation appropriately. That is something lacking in pathology. Now we are going to discuss mechanisms through which PA mediates anti-inflammatory states and disrupts the pro-inflammatory feedback loops.

11.1 Interleukin-6 and its role in inflammation

As we have discussed IL-6 is associated with psychiatric, neurodegenerative and inflammatory disorders. It also gets increased during and short after exercise, it is because it gets released from contracting skeletal muscle during PA and in this context is called myokine (Pedersen *et al.*, 2003). It has been suggested to play a pleiotropic role in metabolism [Reviewed here: (Pal *et al.*, 2014)], but there is also emerging evidence in playing pleiotropic role in inflammation as well (Tilg *et al.*, 1994; Steensberg *et al.*, 2003). Contracting muscles do account for increased levels of IL-6, but it is not necessarily induced by muscle damage, rather than the contraction itself, essentially making it an endocrine organ, it also is not preceded nor accompanied by production of TNFα (Steensberg *et al.*, 2002; UTTER *et al.*, 2007). Muscle contraction induced IL-6 does enter blood and elevates levels of it in plasma (Steensberg *et al.*, 2000). It is worth to note that levels of IL-6 released during PA are also directly linked to both length of the exercise and muscle volume engaged during the exercise. Acute release of IL-6 during and right after exercise (which also goes down 3 hours after PA (Morrison *et al.*, 2018)) accounts for release of anti-inflammatory IL-10 and IL-1 receptor antagonist, which we can also see in intravenous application of endogenous IL-6 along with increased tumor necrosis factor antagonists (TNFsRp55), CRP and cortisol (Tilg *et al.*, 1994;

Steensberg *et al.*, 2003). Interestingly, it has been shown from epidemiological studies that PA is negatively associated with IL-6 plasma levels and CRP, therefore the more physically active, the lower IL-6 plasma and CRP levels (Geffken *et al.*, 2001; Hamer *et al.*, 2012). It could be argued that higher PA causes having less adipose tissue, which is also producer of IL-6 over time (Sindhu *et al.*, 2015), but accounting for confiding factors including BMI still showed significant difference (Hamer *et al.*, 2012), still, lower adipose tissue as a side effect of PA could (it is almost inevitable) contribute to this effect as BMI does not tell us anything about muscle mass/adipose tissue ratio. Although Wedell-Neergaard et al., 2019 have shown that IL-6 plays a role in reducing visceral adipose tissues as a result of exercise. Group that had blocked IL-6 showed less of a degree of visceral adipose tissue loss and diminished some other benefits of exercise compared to control group (Wedell-Neergaard *et al.*, 2019). Taken together, we can see acute release of IL-6 during exercise, or even intravenously shows anti-inflammatory properties and decreases chronically elevated IL-6 which in different context is shown to be pro-inflammatory. The point is that exercise induced cytokine production radically differs from cytokine production in sickness, disease or chronic inflammatory conditions or even stressful environment. PA in this context acts as an inflammatory regulator, with anti-inflammatory properties and potential inducer of homeostasis in pathology.

11.2 HPA and SNS axis

As we have discussed HPA and SNS axes are important in keeping homeostatic state in case of a stressor, they act predominantly in anti-inflammatory manner, although repeated stress can cause disruption, GCs resistance and dysregulation of those axes, which then lead to elevated inflammatory response and unresolved initial stressor. It has been shown that PA can regulate those axes and provide sort of a buffer for future stressors other than the PA itself e.g. psychosocial one (Zschucke *et al.*, 2015; Wunsch *et al.*, 2017). This, in turn, can prevent the pathology inducing over-stimulation in the presence of the same volume and intensity of the stressors.

11.3 Interplay between SIRT1 and NFκB

There is an interplay between the protein deacetylase silencing information regulator (SIRT1) and NFκB pathway. SIRT1 is able to deacetylate components of NFκB complex and suppress NFκB dependent gene expression, on the other hand there is an evidence for both stimulation and inhibition of SIRT1 by NFκB but it is not clear how other factors contribute to mechanisms involved in either suppression or activation, although it seems that NFκB is

more suppressive than expressive from emerging literature, but more evidence is needed (Kauppinen *et al.*, 2013, Huang *et al.*, 2016*a*; Liu *et al.*, 2019). SIRT1 also interacts with FOXO3 transcriptional factors, which then suppresses stress mediated cell-death and might increase stress resistance, though the effects are not fully clear yet as FOXO3 acts differently in various tissues and with different cofactors (Tran *et al.*, 2002). SIRT1 is also important in maintaining mitochondrial content and potentiates mitochondrial biogenesis in the context of exercise (Menzies *et al.*, 2013). SIRT1 is upregulated as a result of PA (Menzies *et al.*, 2013; Huang *et al.*, 2016*b*, *a*; Koo *et al.*, 2017; Taka *et al.*, 2017; Liu *et al.*, 2019), introducing yet another way of decreasing inflammation, mainly through suppression of NFκB pathway. Lack of PA could also play a role in creating positive feedback loop of inflammation through activation of NFκB and its potential suppressive effect on SIRT1. There is another potential inflammatory feedback loop: Sirtuins also play a role in DNA repair, if inflammation is increased then DNA damage occurs (Pálmai-Pallag and Bachrati, 2014), sirtuins sense it and mediate DNA repair, therefore lesser amount of sirtuins are able to suppress pro-inflammatory pathways (Choi and Mostoslavsky, 2014; Jang *et al.*, 2017; Stratigi *et al.*, 2017).

11.4 PGC-1α1 effect on Kynurenine Pathway

Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α1 is upregulated in PA and plays a role in cellular energy metabolism. Agudelo et al., 2014 have shown that PGC-1α1 plays a role in KP, where it upregulates kynurenine aminotransferase (KAT), which leads to conversion of KYN to KYNA in plasma, inhibiting KYN to enter CNS in mice. Not only that, but chronic mild stress induced depressive like behaviour and increased 3-Hydroxykynurenine (metabolite that leads to production of potentially neurotoxic QUIN, figure 1.) in wild type (WT) compared to mice with overexpressed PGC-1α1 (mck-PGC-1α1), moreover injection of KYN also increased depressive behaviour in WT, but not in mck-PGC-1α1 mice suggesting that PGC-1α1 can protect the brain from kynurenine metabolite disbalance, which as we have discussed earlier is linked to pathology. Mck-PGC-1α1 mice were also shown to have diminished effect on increased levels of pro-inflammatory cytokines in hippocampus induced by KYN injection, which also mimicked the effects of

chronic mild stress on the level of KYN in WT mice (Agudelo *et al.*, 2014).

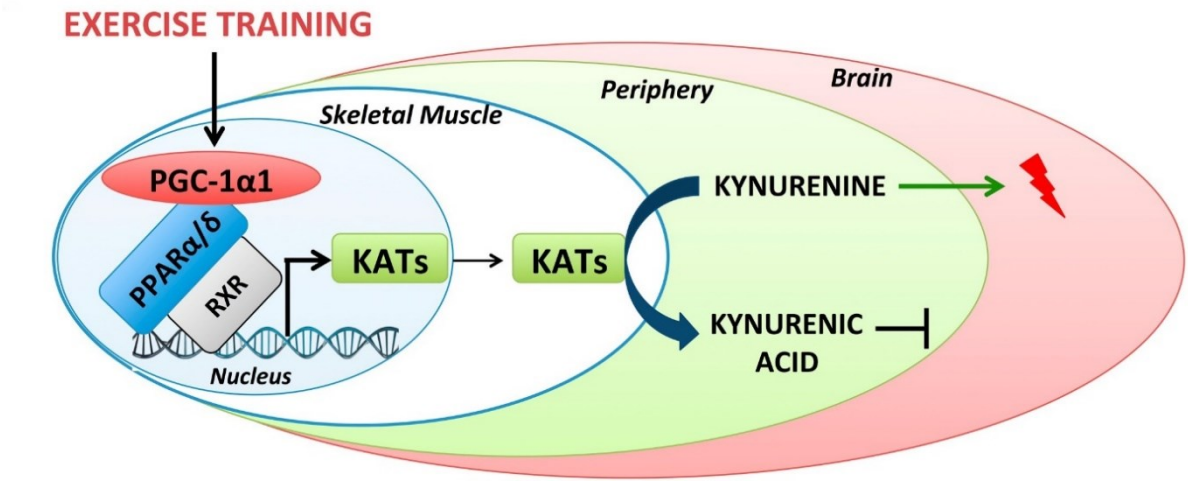

Figure 3: Synoptic figure highlighting the molecular mechanism by which skeletal muscle PGC-1α1 shifts peripheral metabolism of KYN into KYNA [Note: full figure reference in "references", reprinted from (Agudelo *et al.*, 2014)]

11.4.1 FNDC5 effect on BDNF

Fibronectin type III domain-containing protein 5 (FNDC5) is a precursor to irisin and a protein encoded by the gene FNDC5. Wrann et al., 2013 did an amazing study showing that PGC-1α1 regulates expression of neuronal FNDC5, which is suggested to play a role in neuronal development. Both PGC-1α1 and FNDC5 were significantly upregulated in hippocampus of mice after 30 days of voluntary free running exercise, moreover PGC-1α1 and FNDC5 were shown to upregulate BDNF (Wrann *et al.*, 2013). The effect of exercise in upregulating PGC-1α1, FNDC5 and BDNF was specific to hippocampus (Wrann *et al.*, 2013). Increased levels of PGC-1α1 and FNDC5 resulted from PA in human studies as well (Gibala *et al.*, 2009; Egan *et al.*, 2010; Little *et al.*, 2010, 2011; Safdar *et al.*, 2011; Norheim *et al.*, 2014). Taken together PGC-1α1 plays an important role in (apart from many others) keeping the brain healthy, and its upregulation is induced by PA; an overview can be seen in figure 4.

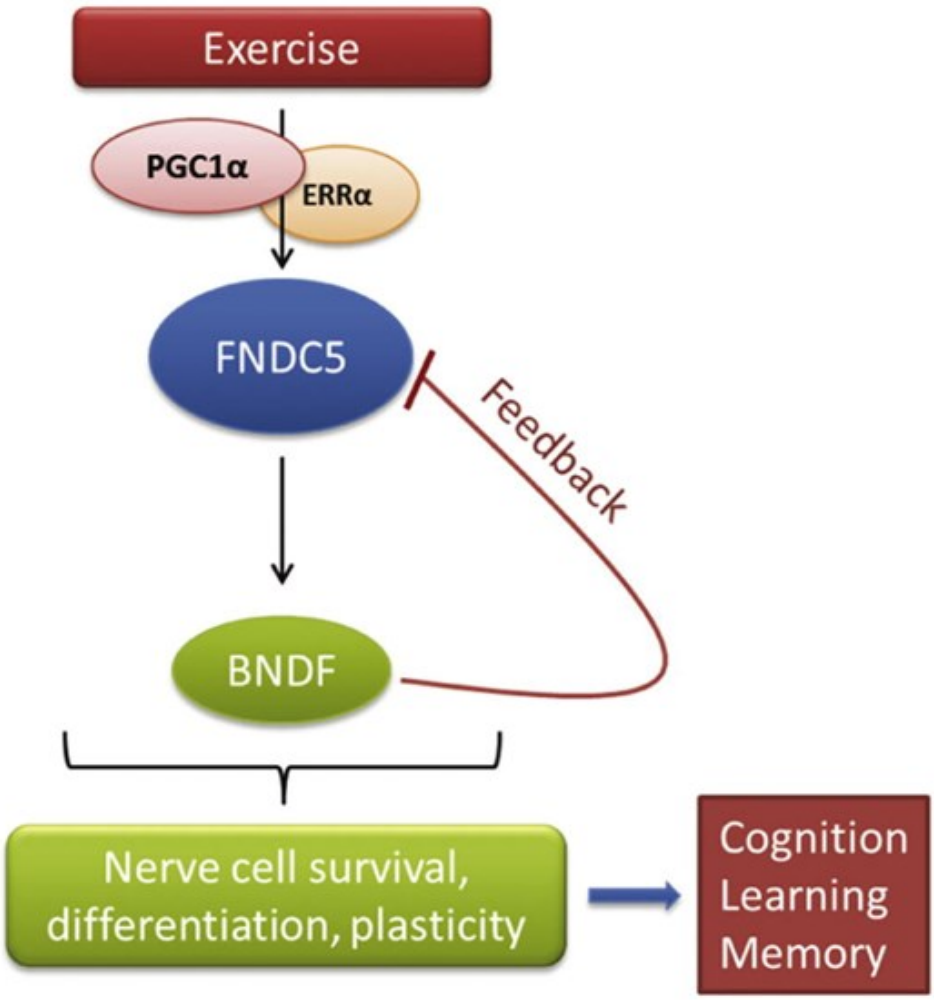

Figure 4: Model of a pathways through which exercise induces BDNF. BDNF is the master regulator of nerve cell survival, differentiation, and plasticity in the brain. This will lead to improved cognitive function, learning, and memory, which are known beneficial effects of exercise on the brain. [Note: full figure reference in "references", from (Wrann *et al.*, 2013)]

11.5 Heat Shock Proteins

Zychowska et al., 2018 have shown that adaptation to heat stress (sauna bathing) occurred with lowering expression of IL-6 mRNA while also increasing IL-10 mRNA, although the effect on IL-6 mRNA was not as significant as on IL-10 mRNA, moreover, this change occurred not only in comparison of a reaction to the first sauna and to last sauna but also during resting period (measured before first sauna and 48 hours after last sauna). The heat stress was introduced by 12 sauna bathing session in 4 weeks (Zychowska *et al.*, 2018). Change in expression of genes coding for heat shock proteins HSP70 and HSP27 was the same as on IL-6 mRNA and IL-10 mRNA respectively. This could suggest that similar

changes are happening on a smaller scale during exercise as there is a heat stress too, which could also be why the individuals with high cardiovascular fitness saw faster changes and better results in their adaptation to heat stress (Zychowska *et al.*, 2018).

11.6 Other exercise induced mechanisms

11.6.1 The role of BDNF

Earlier in the thesis we have shown BDNF effects on neuroplasticity, although that is not everything. BDNF act upon several mechanisms involved in psychiatric diseases. It improves neuroplasticity, learning through enhancing long term potentiation, cell growth and survival. This can directly prevent some of the damage done by inflammation, neurotoxic metabolites or imbalances in KP, which are linked to psychiatric diseases and inflammation. BDNF directly counters these pathologies as they are at least in part mediated by decreased levels of BDNF itself. BDNF is increased during and after exercise (Ferris *et al.*, 2007; Rasmussen *et al.*, 2009; Kimhy *et al.*, 2015; Sleiman *et al.*, 2016), therefore being ideal for prevention and treating of neurodegenerative and psychiatric disorders as PA is also followed by anti-inflammatory context. Szuhany et al., 2015 showed that infusion of BDNF has antidepressant effects and improves performance in an array of tasks in rats. Although I would like to emphasize the importance of context of the PA which I think is important, because BDNF does not choose to enhance learning only at some things, Penzo et al., 2015 have shown that activation of BDNF receptor tropomyosin-related kinase B (TrkB) induces fear conditioning in lateral division of central amygdala in mice. On the other hand, that was shown by either deletion or injection of BDNF, unrelated to PA, also the highest exercise induced BDNF levels are found in hippocampus. Enhanced learning within the framework of PA makes sense from an evolutionary point of view, increased PA was a lot of times in the context of a psychological stressor, such as predator or when hunting for food. Therefore, it was essential to remember the mistakes and threats that would cause not having food, injury or death of a member of a tribe. This could be one of the reasons why we see a lower BDNF response to PA in women (Szuhany *et al.*, 2015), as women did not hunt as much as men for vast majority of the human evolution (Marlowe, 2007; Gurven and Hill, 2009). Exercise upregulates BDNF in hippocampus where it was shown to increase its volume and dendritic density, therefore protecting volume loss in pathology (Bueller *et al.*, 2006; Stranahan *et al.*, 2009; Erickson *et al.*, 2011, Rizos *et al.*, 2011). On the contrary there was a study showing increased BDNF levels while also decreased hippocampal volume in certain regions by 2% in the exercise group compared to the controls, though that might have been due to nature and

intensity of the exercise (Wagner *et al.*, 2015). BDNF was also shown to regulate activity of Nrf2 pathway.

11.6.2 Nrf2 pathway

The Nrf2 pathway is worth mentioning by itself given its role in dealing with oxidative stress and mediating suppression of transcription of pro-inflammatory cytokines (Kobayashi *et al.*, 2016). Bouvier et al., 2017 have shown that acute stress (social defeat) induced vulnerability to depression in 40% of rats, which was associated with persistent oxidative stress state which was mediated by inactivity of Nrf2. Furthermore, they have tested vulnerability to depression of Nrf2 null rats, vulnerability to depression was observed after chronic exposure to stress (3 weeks of chronic mild stress) rather than acute one, this effect was diminished when pre-treated with antioxidants. Vulnerability to depression also diminished after administration of t-BHQ, a compound inducing Nrf2 activity. They also showed that Nrf2 is regulated by BDNF by microinjecting BDNF siRNA into rats hippocampi, which in turn lowered translocation of Nrf2 and increased oxidative stress, on the same note, microinjections of BDNF increased translocation of the Nrf2 (Bouvier *et al.*, 2017). Nrf2 was shown to be increased after exercise (Li *et al.*, 2015; Done *et al.*, 2016; Wang *et al.*, 2016; Abreu *et al.*, 2017). This suggests yet another potent mechanism through which exercise induces anti-inflammatory state and protection against psychiatric disorders.

11.6.3 Effect of exercise on metabolic stress

One way of inducing metabolic stress is over-activation of immune system during inflammatory response, especially when unresolved, therefore chronic inflammation. This can reallocate resources from other organs including brain, which can cause harm especially in development of those organs. There is a mechanism in place, to lower postprandial inflammation in babies, without compromising their immunity. Lactoferrin is found in breast milk and does exactly that, downregulates postprandial immune reaction as well as protects against infection by being immunologically active by itself. Lactoferrin is also produced during and after exercise, which then turns down some of the postprandial immune reaction which is more frequent as the food is more abundant compared to the past. Lactoferrin also stimulates expression of six-transmembrane protein of prostate 2 (STAMP-2) which then downregulates NF-kB pathway inhibiting production of pro-inflammatory cytokines. [From a review by (Pruimboom *et al.*, 2015)]

11.6.4 Angiogenesis in physical activity

If we are talking about metabolic stress, one might argue that PA does put our organs including brain in metabolic stress as well. This would be true, if PA did not promote upregulation of vascular endothelial growth factor (VEGF) which leads to angiogenesis inside the brain, better blood flow and glucose uptake upregulation, allowing the nutrients needed to enter CNS, reducing the metabolic stress in a long run (Ding *et al.*, 2004, 2006; Green *et al.*, 2008; Egan *et al.*, 2010; Berggren *et al.*, 2014; Hirasawa *et al.*, 2016; Morland *et al.*, 2017; Robinson *et al.*, 2018). Therefore, not only does PA attenuate pro-inflammatory states, which induce metabolic stress by itself, but also promote better availability of nutrients and energy to the tissue.

11.6.5 Reduction of stressors themselves

As we have discussed, inflammation is also caused by psychosocial stress, which is an ever-increasing problem in modern society. I would argue that this is where exercise plays its role as well. Firstly, when exercising, it is most likely a time we do not spend being triggered by modern psychosocial stressors; those could be for example information overload, social media and screens, chaos of a city, work and school. Secondly, it is very unlikely, that someone who goes exercise is going to experience fear or anxiety more than if they did not. Some types of exercises might be better as they could force an individual to focus on the exercise and interrupt the negative thinking patterns established in a person with psychiatric disorders, but in people without pathology who experience stress of daily live as well. Regular exercise is also decreasing overall complexity of life that individual experiences by introducing a type of regularity into their schedule, therefore decreasing another stressor.

11.6.6 Role of microRNA

An emerging field of microRNA (miRNA) allows exploration of mechanisms, which were “hidden” from us before. MiRNA are short non-coding RNA molecules. They have ability to activate genes and apart from many regulatory properties, they also affect inflammation. They are both pro- and anti-inflammatory, but there is not enough evidence to support the anti-inflammatory effect of exercise mediated by miRNA, because many times, there are contradicting results from the few studies that had been done (Dufresne *et al.*, 2018; Horak *et al.*, 2018; Improta Caria *et al.*, 2018). Due to lack of literature on miRNAs expression and their effects, only few candidates are worth mentioning such as miRNA 146a, 24, 23b and 181a, which mediate inflammation and exercise affects them, though only miRNA 181a was repeatedly shown to be increased after exercise and act in anti-

inflammatory fashion through suppressing NFκB and negatively regulating TNFα mRNA stability, others miRNAs have shown contradicting effect of exercise on them (Russell and Lamon, 2015; Sapp *et al.*, 2017; Dufresne *et al.*, 2018; Tahamtan *et al.*, 2018). Some of those miRNAs were also shown to be up-regulated in AD e.g. miRNA 146a, it regulates NFκB transcriptional activity and seems to act as a negative feedback mechanism of inflammation, therefore its upregulation is likely due to increased inflammation in AD (Lukiw *et al.*, 2008; Tahamtan *et al.*, 2018). Contradicting results could be an indication of different basal levels of miRNAs and exercise affecting them to promote homeostasis by either up- or down-regulation depending on basal levels that could be sub-optimal, something which could be explored in a future research as understanding of the exercise effect on miRNAs could elucidate some of those questions and help with the treatment strategies.

12 Conclusion

From the evidence, it seems like there is a plethora of mechanisms involved in inflammatory processes and what matters the most is their relative relationship, therefore one of the most important things during IR is the background on which this is happening. Are other stressors such as psychosocial ones involved? What other cytokines which would contribute to reactivation of each other do get released? What situation is the individual in? Does it induce an activation of the brain circuitry related to amygdala? What are the other factors such as BDNF, which would mitigate the decreased plasticity and brain volume as observed in e.g. hippocampus and the PFC in psychiatric disorders? Those are kind of questions we should ask in potential devising of a plan for treating psychiatric diseases with exercise, which I am almost sure is going to come to in the future. If we account the complex mechanisms that stand behind many psychiatric disorders, it would be almost impossible to think of a drug that would affect all of them appropriately. I suggest that as complex as those pathologies are, its prevention and treatment would make sense to be equally as complex, accounting and affecting the vast array of mechanisms at the same time.

12.1 Feedback Loops

This is a reoccurring theme in the research I have done in writing this thesis. Positive pro-inflammatory feedback loops pop up in almost every mechanism we have discussed. This might be also why psychiatric disorders are so hard to treat, because once the inflammation is increased, it is hard to stop the vicious cycle, which also reinforce other feedback loops. This is also why not the acute inflammation is a problem, but constant stimulation of IR, where

first stressors are dealt with fairly well, but subsequent ones are not so, and lead to chronic inflammation. Chronic inflammation is the real problem, because it damages our organism on many levels as discussed in the thesis and now days is also mentioned in the context of neurodegenerative diseases. PA effects being as complex as they are can have profound effect on interrupting inflammatory feedback loops, which underly the pathologies and often overwhelm the homeostatic feedback loops that counteract them. That could lead to much better responsiveness in treating some of those disorders alongside psychotherapy and/or pharmacological treatment.

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